General

Guideline Title

Management of a suspicious adnexal mass.

Bibliographic Source(s)

Dodge J, Covens A, Lacchetti C, Elit L, Le T, Devries-Aboud M, Fung Kee Fung M, Gynecology Cancer Disease Site Group. Management of a suspicious adnexal mass. Toronto (ON): Cancer Care Ontario (CCO); 2011 Jul 7. Various p. (Evidence-based series; no. 4-15). [294 references]

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Recommendations

Major Recommendations

Identification of an Adnexal Mass Suspicious for Ovarian Cancer

- Sonography, particularly three-dimensional (3D) sonography, magnetic resonance imaging (MRI), and computerized tomography (CT) imaging, are each recommended for differentiating malignant from benign ovarian masses. However, the working group offers the following further recommendations, based on their expert consensus opinion and the consideration of availability, access, and harm:
  - Transvaginal sonography should be the first modality of choice, where technically feasible, in patients with a suspicious, isolated ovarian mass.
  - MRI is the most appropriate test to help clarify the malignant potential in patients where ultrasound may be unreliable.
  - CT is most useful in cases where extra ovarian disease is suspected or needs to be ruled out.
- Evaluation of an adnexal mass by Doppler technology alone is not recommended. Doppler technology should be combined with a morphological assessment.
- Ultrasound-based morphological scoring systems can be used to differentiate benign from malignant adnexal masses. These systems are based on specific ultrasound parameters, each with several scores according to determined features. All evaluated scoring systems were found to have an acceptable level of sensitivity and specificity; therefore, the choice of scoring system may be made based on clinician

preference. More information on the characteristics of these scoring systems can be found in Appendix 1 in the original guideline document.
- As a stand-alone modality, serum CA-125 is not recommended for distinguishing between benign and malignant adnexal masses.
- Frozen section for the intraoperative diagnosis of a suspicious adnexal mass is recommended in settings where availability and patient preferences allow.

Surgical Procedures for an Adnexal Mass Suspicious for Malignancy

- Comprehensive surgical staging with lymphadenectomy is recommended for the surgical management of patients with early-stage ovarian cancer to improve survival.
- Laparoscopy is a reasonable alternative to laparotomy, provided appropriate surgery and/or staging can be done. The choice between laparoscopy and laparotomy should be based on patient and clinician preferences. Discussion with a gynecologic oncologist is recommended.
- Fertility-preserving surgery is an acceptable alternative to more extensive surgery in patients with low-malignant potential (LMP) tumours and those with well-differentiated surgically staged 1 ovarian cancer. Discussion with a gynecologic oncologist is recommended.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Suspicious adnexal mass, either symptomatic or asymptomatic

Guideline Category

Assessment of Therapeutic Effectiveness

Evaluation

Management

Treatment

Clinical Specialty

Obstetrics and Gynecology

Oncology

Pathology

Radiology

Surgery

Intended Users

Physicians

Guideline Objective(s)

- To evaluate the optimal strategy for preoperative identification of the adnexal mass suspicious for ovarian cancer
- To evaluate the most appropriate surgical procedure for a woman who presents with an adnexal mass suspicious for malignancy

Target Population

Adult women presenting with a suspicious adnexal mass, either symptomatic or asymptomatic

Interventions and Practices Considered

1. Identification of an adnexal mass suspicious for ovarian cancer
    - Sonography (three-dimensional sonography, transvaginal sonography)
    - Magnetic resonance imaging (MRI)
    - Computerized tomography (CT) imaging
    - Doppler technology combined with morphological assessment
    - Use of ultrasound-based morphological scoring systems
    - Serum CA-125 (not recommended as stand-alone modality)
    - Frozen section for the intraoperative diagnosis of a suspicious adnexal mass
2. Surgical procedures for an adnexal mass suspicious for malignancy
    - Comprehensive surgical staging with lymphadenectomy in patients with early-stage ovarian cancer
    - Laparoscopy as a reasonable alternative to laparotomy
    - Fertility-preserving surgery as an acceptable alternative to more extensive surgery

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests
- Optimal surgery
- Overall survival
- Disease-free survival
- Progression-free survival
- Reduction in the number of surgeries
- Morbidity
- Adverse events
- Quality of life

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategy

Environmental Scan

As a first step, an internet search of Canadian and international health organizations and the National Guideline Clearinghouse (see Appendix 1 in

the original guideline document for full list) was conducted for existing guidelines and systematic reviews relevant to the research question. Guidelines were included if they were published since 1999 in English. This initial environmental scan yielded 11 practice guidelines; however, one guideline was excluded because the full guideline was available only in French, and another guideline was excluded because only the National Guideline Clearinghouse summary was available. One evidence report/technology assessment and one clinical practice guideline identified through this environmental scan were deemed to be the most appropriate to answer the guideline questions. The 2006 Agency for Healthcare Research and Quality (AHRQ) report addressed the identification of an adnexal mass suspicious for malignancy question. The 2004 Australian Cancer Network (ACN) Clinical Practice Guideline addressed the surgical management of an adnexal mass suspicious for malignancy question.

Update Literature Search Strategy

The literature search from the AHRQ report was updated (see Appendix 2 in the original guideline document) using MEDLINE (OVID: January 2004 through week 3, March 2009). In addition, as an exact search strategy for the Australian Cancer Network report was not available, an update of that literature search (see Appendix 2 in the original guideline document) was approximated using the keywords provided in the report using MEDLINE (OVID: January 2004 through week 3, April 2009). This literature search combined disease-specific terms ('pelvic mass,' 'adnexal mass,' 'pelvic neoplasms,' 'ovarian cancer,' 'ovarian neoplasm,' 'ovarian carcinoma,' 'epithelial ovarian cancer,' 'borderline ovarian tumours' and 'tumours of low malignant potential') with surgical specific terms ('intraoperative pathological examination,' 'frozen section,' 'debulking surgery,' 'fertility sparing,' 'surgical staging,' 'bilateral salpingo-oophorectomy,' 'total hysterectomy,' 'node or nodal dissection,' 'surgical management,' 'treatment,' 'cytoreduction,' 'secondary cytoreduction,' 'interval cytoreduction,' 'laparotomy,' and 'laparoscopy') for all study designs.

Relevant articles and abstracts were selected and reviewed by two reviewers. The reference lists of included studies along with the personal reference lists of the guideline working group were searched for additional studies.

Study Selection Criteria

Articles were eligible for inclusion in this systematic review if they were systematic reviews, meta-analyses, clinical practice guidelines, randomized trials, or comparative cohort studies. Studies identified in the update of the AHRQ report literature search were included based on the same inclusion criteria put forth in the AHRQ report.

For studies investigating single modality identification of an adnexal mass, the inclusion criteria were:

1. Comparison of the test (e.g., bimanual pelvic exam or ultrasound, to histology or negative surgery)
2. Greater than 20 patients included in study
3. Able to construct a 2-by-2 table, which compares the results of the diagnostic test with the definitive histological diagnosis

For studies investigating the use of multi-modality scoring systems (i.e., Risk of Malignancy Index [RMI]), the inclusion criteria were:

1. Patients with suspicion of cancer
2. Studies with scoring, risk score, combined modality approach
3. Assesses predictive value of two or more variables using multivariable model
4. Greater than 50 patients included in study

Studies identified in the update of the Australian Cancer Network guideline were based on the following selection criteria:

1. Greater than 20 patients included in study
2. Patients with an adnexal mass suspicious for early stage (I-II) malignancy,
3. Two-armed (or greater) study design with a comparison of surgical procedures/techniques/approaches
4. Report on at least one of the following outcomes: optimal surgery, overall survival, progression-free or disease-free survival, reduction in the number of surgeries, morbidity, adverse events, quality of life

Number of Source Documents

Identification of an Adnexal Mass Literature

Four meta-analyses and 67 primary studies, pertaining to the identification of an adnexal mass suspicious for malignancy, met the inclusion criteria and are included in this review.

Surgical Procedures Literature

A total of 1809 articles were identified in the updated search for the most appropriate surgical procedure, of which 16 met the inclusion criteria.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Synthesizing the Evidence

A bivariate, random-effects meta-regression model was used to produce summary estimates of sensitivity and specificity and to plot summary receiver operating characteristic (ROC) curves with 95% confidence regions. This model, described in detail elsewhere, has several advantages over the standard summary ROC approach. Chief among these is the preservation of the two-dimensional nature of the data and the incorporation of any correlation that might exist between sensitivity and specificity. The model assumes that the logit sensitivities and specificities are normally distributed and makes use of the variance estimates to compute study weights. Heterogeneity in the current review was assessed visually. Given that between-study heterogeneity is widespread for measures of diagnostic accuracy, a random-effects model was used for all pooling. This bivariate, random-effects model takes into account the difference in precision by which sensitivity and specificity have been measured within and across studies, and it incorporates and estimates the amount of between-study variability. Statistical analyses were executed with the statistical software package STATA version 11 using the metandi command. The outcomes of the meta-analyses were plotted as summary ROC curves and can be seen in Figures 2A-D in the original guideline document.

The Gynecology Cancer Disease Site Group (DSG) decided not to pool the surgical studies, but rather to present the results of each study individually in a descriptive fashion.

Quality Appraisal and Data Extraction

The Appraisal of Guidelines Research and Evaluation (AGREE) tool was used to evaluate the quality of identified evidence-based guidelines. While all scoring domains of the AGREE tool were considered in the evaluation of guidelines, the Rigour of Development domain, describing the rigour of systematic methods in identifying and evaluating evidence, was considered to be most relevant in application for this systematic review. Systematic reviews and meta-analyses were assessed for quality using the AMSTAR tool. The quality of primary studies included assessments for study design, type of data collection, sampling method, and blinding.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Evidence-Based Series (EBS) guidelines developed by the Cancer Care Ontario Program in Evidence-Based Care (CCO PEBC) use the methods of the Practice Guidelines Development Cycle. For this project, the core methodology used to develop the evidentiary base was an update of two previously published systematic reviews: the Agency for Healthcare Research and Quality (AHRQ) report, 2006, and Australian Cancer Network (ACN) Clinical Practice Guideline, 2004. Evidence was selected and reviewed by five members of the PEBC Gynecology Cancer Disease Site Group (DSG) and one methodologist.

The systematic review is a convenient and up-to-date source of the best available evidence on the management of an adnexal mass suspicious for malignancy. The body of evidence in this review is primarily comprised of prospective and retrospective cohort studies. That evidence forms the basis of the recommendations developed by the Gynecology Cancer DSG and published in Section 1 of the original guideline document. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Report Approval Panel

Prior to the submission of this Evidence-Based Series (EBS) draft report for external review, the report was reviewed and approved by the Program in Evidence-Based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the Gynecology Cancer Disease Site Group (DSG) circulated Sections 1 and 2 to external review participants for review and feedback.

Methods

Targeted Peer Review: During the guideline development process, two targeted peer reviewers from Ontario and one from the United States of America (USA) considered to be clinical and/or methodological experts on the topic were identified by the working group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on April 8, 2011. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call).

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Gynecologists and gynecologic oncologists in the PEBC database were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1 in the original guideline document) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1 in the original guideline document) and the evidentiary base (Section 2 in the original guideline document). The notification email was sent on April 13, 2011. The consultation period ended on June 10, 2011. The working group reviewed the results of the survey.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Gynecology Cancer Disease Site Group, and the Report Approval Panel of the PEBC.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by meta-analyses, comparative cohort studies (prospective and retrospective), and randomized controlled trials.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Identification of an Adnexal Mass Suspicious for Ovarian Cancer

- A meta-analysis of six cohort studies that investigated three-dimensional (3D) sonography indicated an enhanced sensitivity of 93.5% and specificity of 91.5% with 3D technology.
- A meta-analysis of 22 cohort studies with 24 data sets that investigated the effectiveness of magnetic resonance imaging (MRI) in the diagnosis of adnexal masses found an overall sensitivity of 91.9% and specificity of 88.4%.
- A meta-analysis of seven studies with eight data sets considering computed tomography (CT) technology yielded an overall sensitivity of 87.2% and specificity of 84.0%.
- A meta-analysis of the resistance index (RI) included 35 cohort studies with 42 data sets and yielded an overall sensitivity of 77.2% and specificity of 89.8%.
- A meta-analysis of 21 cohort studies with 22 data sets that evaluated the pulsatility index (PI) found an overall sensitivity of 80.6% and specificity of 79.9%.
- A meta-analysis of the peak systolic velocity (PSV) included seven cohort studies and found an overall sensitivity of 80.0% and specificity of 84.2%.
- Direct comparisons between ultrasound-based morphological scoring systems were not performed in this review. Instead, the assessment was based on summary data on sensitivity and specificity obtained from the meta-analyses conducted. The meta-analyses found summary sensitivities ranging from 83.5% to 91% and specificities ranging from 63% to 85.9%.
- The Risk of Malignancy Index (RMI) is a clinical prediction rule that includes CA-125 and menopausal status, in addition to ultrasound-based morphology. In a meta-analysis of data from the 13 RMI studies, with 15 data sets, employing a cutoff of 200 to be indicative of malignancy, the summary sensitivity and specificity were 79.2% and 91.7%, respectively. RMI2 and RMI3 are newer versions of this tool, with comparable levels of sensitivity and specificity. The choice of version of RMI should be based on clinician preference.
- The recommendation against using serum CA-125 as a stand-alone modality, is based on a meta-analysis of 49 cohort studies and two case-control studies with a total of 52 data sets that found, at a threshold of 35 U/mL, an overall sensitivity of 78.7% and specificity of 77.9%.
- The recommendation for the use of frozen sections for the intraoperative diagnosis of a suspicious adnexal mass is based on a meta-analysis of frozen section diagnoses that included 15 cohort studies and yielded an overall sensitivity of 89.2% and specificity of 97.9%.

Surgical Procedures for an Adnexal Mass Suspicious for Malignancy

- Two large population-based studies found that surgical staging with lymphadenectomy was associated with improved three-year ($p<0.001$) and five-year disease specific survival ($p<0.001$) compared to staging procedures without lymphadenectomy.
- One study reported a statistically significant improvement in five-year overall survival rates in patients undergoing a lymphadenectomy versus those that did not (87% vs. 64%, respectively; $p=0.02$).
- Survival analyses also demonstrated a statistically significant benefit in disease-free survival ($p=0.004$ and $p=0.0007$, respectively) for patients undergoing a lymphadenectomy versus those that did not.
- In another study that considered overall survival, researchers reported a statistically significant difference ($p=0.0008$) in the two patient

groups in favour of the patients undergoing a lymphadenectomy.

- One randomized controlled trial (RCT) was identified and reported no statistically significant effect of lymphadenectomy on progression-free (hazard ratio [HR]= 0.72; 95% confidence interval [CI], 0.46 to 1.14) or overall (HR=0.85; 95% CI, 0.49 to 1.47) survival. However, this study was underpowered to detect a difference in survival, the study's secondary outcome. Rather, the sample-size calculation for this RCT was undertaken to detect a difference in prevalence of lymph node positivity. It was deemed inadequate to inform the recommendation.
- In the three studies that considered patients with early epithelial ovarian cancer, no statistical difference in survival rates was detected between patients undergoing a laparoscopy versus laparotomy.
- In the management of patients with early borderline ovarian tumours, two studies found that a laparoscopic versus laparotomic surgical approach did not appear to influence survival rates.
- One cohort study specifically compared rates of recurrence in 40 patients who underwent unilateral salpingo-oophorectomy versus 22 patients who underwent cystectomy only. No statistical difference in recurrence rates was detected (27.5% vs. 22.7%, respectively; p=0.8). Similarly, in a larger study of 360 women with LMP tumours, another cohort study found no difference in disease-free survival between patients who underwent radical or fertility-sparing surgery (p=0.651).

Potential Harms

- While the surgical technique does not appear to impact patient survival, there have been differences detected in surgical outcomes and complication rates. One study found a statistically significant difference in complication rates, with 12.9% experiencing a complication in the completely staged group versus 1.0% in those incompletely staged (p<0.001). Another study reported a statistically significant difference in the rates of minor postoperative complications, with 6.7% of patients in the laparoscopy group experiencing such an event compared to 42.1% of patients in the laparotomy group (p=0.047).
- One group of researchers reported a difference in the cases of tumour rupture or spilling during surgery, with 34.6% ruptures recorded in the laparoscopic group compared to 6.6% in patients undergoing a laparotomy (p<0.0001). Similarly, another research group found 31% of laparoscopic patients experienced intraoperative tumour rupture versus 16% in the laparotomy group. However, this difference did not reach statistical significance. In patients with borderline tumours, the difference in the occurrence of intraoperative tumour rupture was found not to be statistically associated with the surgical approach.

Qualifying Statements

Qualifying Statements

- Assessment of an adnexal mass by colour Doppler technology, using the resistance index (RI), pulsatility index (PI), and peak systolic velocity (PSV) indices, was neither as sensitive nor specific as simple ultrasonography. Furthermore, because of the overlap of vascular parameters between malignant and benign masses, a firm diagnosis based on Doppler evaluation alone can be problematic.
- Elevated serum CA-125 levels have been reported in a variety of benign conditions. Because the incidence of ovarian cancer relative to benign gynecologic conditions is lower in premenopausal women, CA-125 values are of limited use in this population. CA-125 levels are elevated in only 50% of early stage ovarian cancers. Caution should be used in interpreting values in such patients.
- The Gynecology Cancer Disease Site Group (DSG) acknowledges that, despite definitions and criteria, it is unrealistic to expect that 100% of ovarian cancers will be identified as suspicious preoperatively. Pathology remains the gold standard.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician.
- Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Dodge J, Covens A, Lacchetti C, Elit L, Le T, Devries-Aboud M, Fung Kee Fung M, Gynecology Cancer Disease Site Group. Management of a suspicious adnexal mass. Toronto (ON): Cancer Care Ontario (CCO); 2011 Jul 7. Various p. (Evidence-based series; no. 4-15). [294 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Jul 7

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-Based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-Based Care (PEBC) is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Guideline Committee

Gynecology Cancer Disease Site Group

Composition of Group That Authored the Guideline

For a current list of past and present members, please see the Cancer Care Ontario Web site .

Financial Disclosures/Conflicts of Interest

No conflicts of interest were declared for J Dodge, A Covens, C Lacchetti, L Elit, T Le, M Devries-Aboud, or M Fung Kee Fung.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site .

Availability of Companion Documents

The following is available:

- Program in evidence-based care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2011. 15 p. Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site .

Patient Resources

None available

NGC Status

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